An Efficient Asymmetric Synthesis of 1-Acyl-2-alkyl-1,2-dihydropyridines

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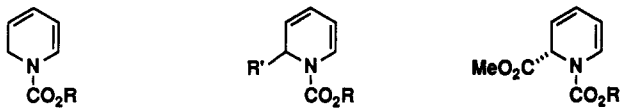
Summary: Two efficient chiral auxiliary mediated asymmetric syntheses of synthetically useful 1-acyl-2-alkyl-1,2-dihydropyridines are described.

For many years there has been considerable interest in the synthesis, synthetic utility, and biological activity of various dihydropyridines.[1] The ability of an *N*-acyl substituent to stabilize[2] the dihydropyridine system has encouraged the use and study of 1-acyldihydropyridines as synthetic intermediates. Several 2-unsubstituted 1-(alkoxycarbonyl)-1,2-dihydropyridines **1** have proven to be useful dienes for the Diels–Alder reaction and have been utilized by several research groups for the synthesis of natural products,[1] particularly the iboga type indole alkaloids.[3] Various 2-substituted 1-acyl-1,2-dihydropyridines **2** are also useful intermediates for the preparation of natural products, such as piperidine,[4] indolizidine,[5] quinolizidine,[6] and *cis*-decahydroquinoline[7] alkaloids.

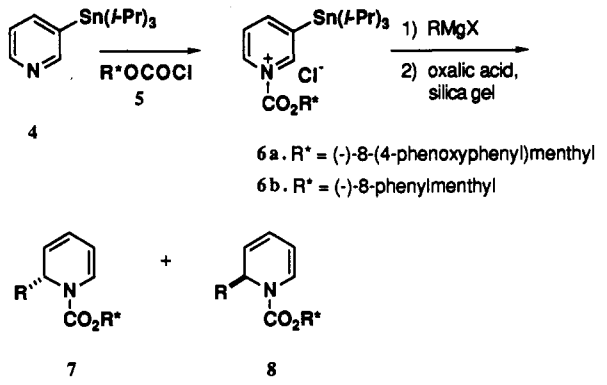


1 **2** **3**

Despite their obvious potential, no reports have appeared on the asymmetric synthesis of 1,2-dihydropyridines **2**. The reported alkaloid syntheses from dihydropyridines **2** are all racemic due to the lack of methodology available for the enantioselective preparation of these heterocycles.[8] Shono has published one example of an enantioselective synthesis of 1,2-dihydropyridine **3** in seven steps from L-lysine.[9] We decided to explore an enantioselective approach to dihydropyridines **2** which involves the addition of Grignard reagents to chiral 1-acylpyridinium salts. We describe herein an efficient chiral auxiliary mediated asymmetric synthesis of several 2-substituted 1-acyl-1,2-dihydropyridines.

We chose 3-(triisopropylstannyl)pyridine (**4**) as the starting material, for it is clear from our recently developed

Scheme I



Scheme II

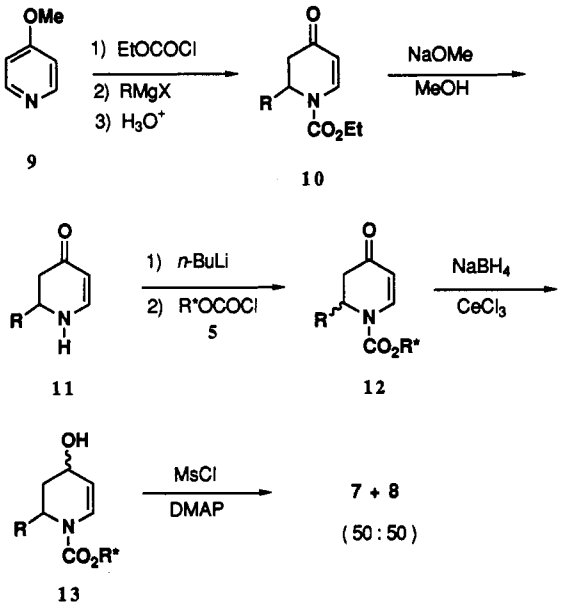


Table I. Synthesis of 1-Acyl-2-alkyl-1,2-dihydropyridines 7

entry[a]	R*OCOCl[b]	RMgX	product	yield,[c] %	de[d]
a	**5a**	*n*-PrMgCl	**7a**	72	82
b	**5b**	*n*-PrMgCl	**7b**	81	78
c	**5a**	*c*-HexMgCl	**7c**	81	91
d	**5a**	$PhCH_2MgCl$	**7d**	58	76
e	**5a**	VinylMgBr	**7e**	71	90
f	**5a**	PhMgCl	**7f**	85	89
g	**5b**	PhMgCl	**7g**	87	84
h	**5a**	*p*-MePhMgBr	**7h**	86	92[e]

[a] The reactions were generally performed on a 0.5-mmol scale using 1.3–1.5 equiv of pyridine **4**. [b] Chiral auxiliary **5a** is (−)-8-(4-phenoxyphenyl)menthyl chloroformate; **5b** is (−)-8-phenylmenthyl chloroformate. [c] Yield of products obtained from radial preparative-layer chromatography. No attempt was made to remove the minor diastereomer **8**. [d] Unless indicated the diastereomeric excess (de) was determined by HPLC. [e] The de was determined by 300-MHz ^1H NMR analysis.

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(7) (a) Comins, D. L.; Abdullah, A. H.; Smith, R. K. *Tetrahedron Lett.* **1983**, *24*, 2711. (b) Comins, D. L.; Abdullah, A. H. *Tetrahedron Lett.* **1986**, *26*, 43. (c) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1991**, *32*, 5697.

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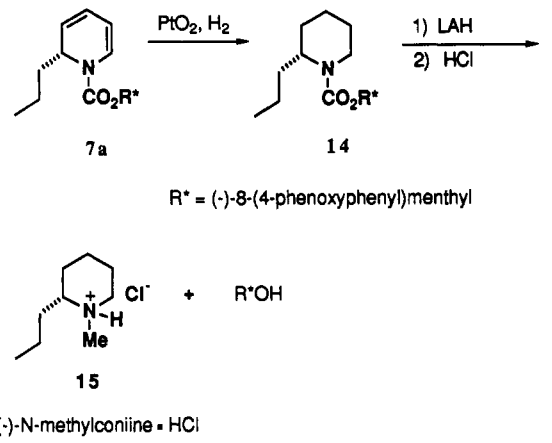
Scheme III

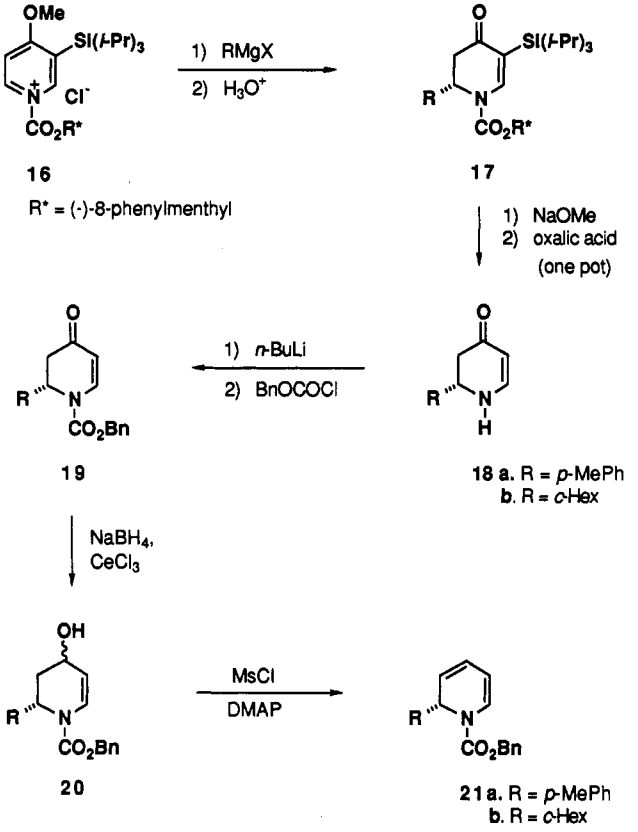


asymmetric synthesis of 2-alkyl-2,3-dihydropyridones[10] that a large blocking group at C-3 of the chiral pyridinium salt is necessary for high diastereoselectivity. Unlike chiral 2,3-dihydro-4-pyridones,[10] the 1-acyl-1,2-dihydropyridines are sensitive to acid, and a blocking group at C-3 would have to be removed under very mild conditions. The triisopropylstannyl group appeared to be ideal for it is bulky enough to block attack by the Grignard reagent at the C-2 and C-4 positions, and it is easily removed from the 1,2-dihydropyridine ring system with oxalic acid.[11]

The chiral 1-acylpyridinium salts **6** were prepared in situ from 3-(triisopropylstannyl)pyridine[12,13] (**4**) and an enantiopure chloroformate **5** derived from (−)-8-phenylmenthol[14] or (−)-8-(4-phenoxyphenyl)menthol.[15] Reaction of the chiral 1-acyl salt **6** with a Grignard reagent followed by treatment of the reaction mixture with silica gel containing oxalic acid provided chiral 1,2-dihydropyridines **7** and **8** in one step from **4** (Scheme I). Several reactions were performed and the diastereomeric excess (de) was determined by HPLC or ^{1}H NMR analyses. The results of this study are given in Table I. For comparison, 50/50 mixtures of diastereomers **7** and **8** were prepared as shown in Scheme II. Racemic **10** was prepared from 4-methoxypyridine, ethyl chloroformate, and a Grignard reagent.[6a] Reaction of **10** with sodium methoxide/methanol gave racemic **11**, which was treated with *n*-butyllithium and chiral chloroformate **5** to give a 50:50 mixture of diastereomers **12**.[10] Reduction of **12** with $NaBH_4/CeCl_3$ provided alcohol **13**. Dehydration using Furukawa's reagent[16] gave the desired 50:50 mixture of dihydropyridines **7** and **8**.

The diastereoselectivity of the Grignard additions to 1-acylpyridinium salts **6** ranged from 76 to 92%. In two examples studied, entries a,b and f,g, the de's obtained were higher when (−)-8-(4-phenoxyphenyl)menthyl chloroformate was used as compared to (−)-8-phenylmenthyl chloroformate. The absolute stereochemistry at C-2 of the 2-phenyl derivatives (**7**, R = Ph) was determined to be *S* by comparison to an authentic sample prepared from (*S*)-2-phenyl-2,3-dihydro-4-pyridone[10] via a three-step sequence analogous to the conversion of **11** to **7** shown in Scheme II. The 2-alkyl derivatives (**7**) were determined to have the *R* configuration at C-2 by a similar procedure.

Scheme IV



A limitation of this one-step enantioselective synthesis is that, unlike chiral 1-acyl-2,3-dihydro-4-pyridones,[10] the chiral auxiliary of **7** is difficult to remove due to the sensitive nature of the dihydropyridine ring system. Reductive removal at a later stage of a synthetic sequence is feasible, however, as is demonstrated by the conversion of **7a** to (−)-*N*-methylconiine as shown in Scheme III. Catalytic hydrogenation of **7a** over PtO_2 gave an 89% yield of 1-acylpiperidine **14**. Reduction of **14** with LAH in THF provided a 70% yield of *N*-methylconiine hydrochloride (**15**) (mp 190–191.5 °C (lit.[17] mp 191–192 °C); $[\alpha]^{24}_D$ −26.5° (*c* 0.81, EtOH) (lit.[18] $[\alpha]_D$ −27.2° (*c* 8.4, EtOH)) and an 86% yield of recovered chiral auxiliary ((−)-8-(4-phenoxyphenyl)menthol). Using this methodology, *N*-methylconiine was prepared enantioselectively in three steps from 3-(triisopropylstannyl)pyridine (**4**).

Since the presence of the chiral auxiliary in **7** may interfere with certain transformations, a second asymmetric synthesis of 1,2-dihydropyridines was developed as shown in Scheme IV.

The chiral 1-acylpyridinium salt **16**, prepared in situ from 4-methoxy-3-(triisopropylsilyl)pyridine and (−)-8-phenylmenthyl chloroformate, was treated with RMgX to give dihydropyridone **17** (R = *p*-MePh, c-Hex) in high yield and high de.[10] The chiral auxiliary and the triisopropylsilyl group were removed from purified diastereomers **17** with sodium methoxide/methanol and oxalic acid to give enantiopure dihydropyridones **18a** (88%) and **18b** (81%) via a one-pot reaction. Deprotonation of **18** with *n*-butyllithium and addition of benzyl chloroformate provided **19** in near quantitative yield. Reduction of **19**

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(12) The 3-(triisopropylstannyl)pyridine (**4**) was prepared in 64% yield from 3-lithiopyridine and triisopropyltin chloride.[13]
(13) Banks, C. K. U.S. Pat. 3,297,732, 1967.
(14) Optically pure (−)-8-phenylmenthol was purchased from Aldrich Chemical Co., Inc. or prepared by a literature procedure, see: Ort, O. *Org. Synth.* **1987**, *65*, 203.
(15) d'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112.
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(17) Ahrens, F. B. *Chem. Ber.* **1902**, *35*, 1330.
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to alcohols **20** and subsequent dehydration gave the desired enantiomerically pure 1-(benzyloxycarbonyl)-1,2-dihydropyridines **21a** [$[\alpha]^{23}_D$ −524 (*c* 0.42, $CHCl_3$)] and **21b** [$[\alpha]^{23}_D$ −696 (*c* 1.5, $CHCl_3$)] in 58 and 74% yield, respectively.[19,20]

The door has now been opened to the enantioselective synthesis of various alkaloids via chiral 1-acyl-1,2-dihydropyridine intermediates. Additional studies on the synthesis and synthetic utility of these chiral heterocycles are in progress.

Acknowledgment. We gratefully acknowledge support of this work by the National Institutes of Health and North Carolina State University.

Supplementary Material Available: Experimental details for the preparation of **7a** and **21a** and physical data for **7**, **15**, and **21a,b** (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(19) Dihydropyridines **21** of the opposite configuration can be prepared by using (+)-8-phenylmenthol as the chiral auxiliary. For a procedure on the preparation of 28 g of (+)-8-phenylmenthol, see: Buschmann, H.; Scharf, H.-D. *Synthesis* **1988**, 827.

(20) All new compounds were spectroscopically characterized and furnished satisfactory elemental analyses (C,H,N, ± 0.4%) or high-resolution mass spectra. Details are provided in the supplementary material.

The Asymmetric Metalation of Chiral Arylaldehyde Acetal Chromium Tricarbonyl Complexes

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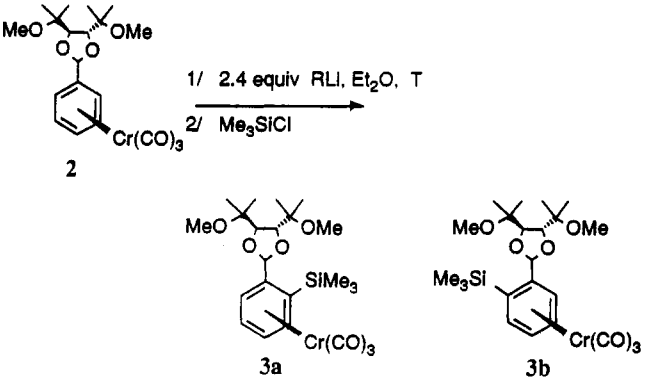
Summary: The chiral chromium tricarbonyl complex of benzaldehyde acetal **2**, derived from (+)-diethyl tartrate, can be metalated by *n*-BuLi and subsequently functionalized by various electrophiles with a minimum of 86% de.

The use of chromium tricarbonyl arene complexes in the synthesis of optically pure compounds has great potential.[2] Especially useful are the complexes of ortho-disubstituted arylaldehyde derivatives, as the chemistry of the carbonyl function in such molecules has been investigated in some depth and many highly asymmetric transformations have been revealed.[3] To this point, the field has been hampered by the limited availability of enantiomerically pure material. Preparation of enantiomerically enriched complexes of this type has been accomplished by classical or kinetic resolution of racemic mixtures.[4] Asymmetric synthesis of such compounds has been restricted to the α-phenethylamine- or ephedrine-derived substrates, which undergo highly diastereoselective ortho metalation[5-7] but where the chiral auxiliary is not readily removable.

We were intrigued by the possibility of accomplishing asymmetric directed metalation of a monosubstituted arene–$Cr(CO)_3$ complex modified with a removable chiral

Table I. Variation of Base and Conditions on Diastereoselectivity



base	*T* (°C)	yield (%)	3a:3b	de (%)
t-BuLi	−78	60	50:50	0
	−30	20	34:66	−32
MeLi[a]	−78	5	77:23	54
	−30	50	87:13	74
n-BuLi	−78	80	84:16	68
	−30	75	88:12	76
	−30[b]	90	93:7	86

[a] Low halide concentration (1.4 M MeLi, 0.05 M in halide). [b] Slow addition of *n*-BuLi (2.4 equiv over 1.5 h).

(1) (a) Current address: Department of Heterocyclic Chemistry, Pharmaceutical Institute, Tokohu University. (b) NSERC (Canada) University Research Fellow 1989–1994.

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(3) (a) Solladié-Cavallo, A.; Quazzotti, S.; Colonna, S.; Manfredi, A. *Tetrahedron Lett.* **1989**, *30*, 2933. (b) Solladié-Cavallo, A.; Quazzotti, S. *Synthesis* **1991**, 177. (c) Brocard, J.; Mahmoudi, M.; Pelinski, L.; Maciejewski, L. *Tetrahedron* **1990**, *46*, 6995. (d) Baldoli, C.; Del Buttero, P.; Maiorana, S. *Tetrahedron* **1990**, *46*, 7823. (e) Solladié-Cavallo, A.; Bencheqroun, M. *J. Organomet. Chem.* **1991**, *403*, 159. (f) Mukai, C.; Cho, W.; Kim, I. J.; Kido, M.; Hanaoka, M. *Tetrahedron Lett.* **1990**, *31*, 6893. (g) Mukai, C.; Cho, W. J.; Kim, I. J.; Kido, M.; Hanaoka, M. *Tetrahedron* **1991**, *47*, 3007. (g) Roush, W. R.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 1143. (h) Harrington, P. J. *Transition Metals in Total Synthesis*; John Wiley and Sons: New York, 1990; Chapter 11.

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